UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/256,156	02/24/1999	STEPHEN GILLIES	LEX-003	9492

22832 7590 06/21/2005

KIRKPATRICK & LOCKHART NICHOLSON GRAHAM LLP
(FORMERLY KIRKPATRICK & LOCKHART LLP)
75 STATE STREET
BOSTON, MA 02109-1808

EXAMINER	
GALVEZ, JAMES JASON	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/256,156	GILLIES ET AL.	
	Examiner	Art Unit	
	J. Jason Galvez	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,6-8,10,27,29 and 30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4,6-8,10,27,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3\30\05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

The amendment filed 3/30/2005 has been made of record. Claims 1, 4, 6-8, 10, 27 and 29-30 are pending and under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

It is noted that claims 1, 6-8, 10 and 29-30 are drawn to non-elected subject matter. The originally elected invention was drawn to antibody-based fusion proteins, not polynucleotides, *i.e.* "a gene construct" (see office action dated: 08/29/2000). However in an effort to promote compact prosecution, the examination and search of the invention has been conducted to read on antibody-based fusion proteins. If Applicant does not amend, or wish to amend, the claims to read on the originally elected inventions the claims will be precluded from examination.

Objections/Rejections: Withdrawn

Claim Rejections - 35 USC § 112, 1st paragraph

The rejection of claims 1, 6-8, 10, 27, 29 and 30 for not meeting the enablement requirement under 35 U.S.C. § 112, first paragraph, has been withdrawn in response to Applicant's amendment to the claims.

The rejection of claims 1, 6-8, 10, 27, 29 and 30 for not meeting the written description requirement under 35 U.S.C. § 112, first paragraph, has been withdrawn in response to Applicant's amendment to the claims.

Objections/Rejections: Maintained/New Grounds

Information Disclosure Statement

The information disclosure statement filed 3/30/2005 has been considered. However, it is noted that the information disclosure statement cites many references appearing to have no relevance to the instant case. For example, there are numbers of references relating to erythropoietin, which appears to be irrelevant in the instant case.

Claim Rejections - 35 USC § 103

The rejection of claims 1, 3, 6-8, 10, 27, 29 and 30, now applied to claims 1, 6-8, 10, 27, 29 and 30, as being unpatentable under 35 U.S.C. § 103(a) over Gillies *et al.* in view of Gray *et al.* is maintained for the reasons of record in the previous office action (mail date: 09/30/2004). Applicant argues that combining the references would not make the instant invention obvious in view of the prior art. Particularly, Gray *et al.* do not teach modifications of CH2 domains to increase the half-life of immunoglobulin fusion proteins. Applicant also argues the recitation by Gray *et al.* of "display a long plasma half-life *in vivo*", in reference to fusion proteins with mutated immunoglobulin regions, is not the same as the instant invention of fusion proteins with "a longer half-life than fusion proteins without the mutations". Applicant further argues Gray *et al.* has no indication of properties "appreciated or taught" relating to increased half-life. Applicant supports arguments regarding unappreciated and untaught properties of increase half-life by citing teaching by Gray *et al.* of no difference in half-life between CTLA4-IgG1 and CTLA4IgG4. As such Applicant argues a person of ordinary skill in the art would

not be motivated to combine the teachings of Gillies *et al.* and Gray *et al.* Furthermore, Applicant argues the teaching of Gillies *et al.* and Gray *et al.* teach away from each other because Gillies *et al.* teach fusion proteins that are immunostimulatory and Gray *et al.* teach fusion proteins designed to be immunoinhibitory. Finally, Applicant argues claims 27 is particularly not unpatentable over Gillies *et al.* and Gray *et al.* because there is no motivation to combine the teachings and Gray *et al.* never teach antibody-based fusion proteins comprising a IgG4 CH2 domain would have a longer half-life than the same fusion protein comprising a IgG1 CH2 domain instead of a IgG4 CH2 domain.

Arguments presented by Applicant have been fully considered, but have not been found persuasive. Applicant's assertion that Gray *et al.* do not teach increased half-life of modified CH2 domains is incorrect. Gray *et al.* clearly teach the effect of decreased Fc receptor interaction (column 4: lines 24-28). Whether appreciated or not by Gray *et al.*, decreasing Fc receptor interactions would increase half-life of fusion proteins comprising modified CH2 domains. Ravetch *et al.* teach Fc receptors are involved in determining the half-life of immunoglobulins, and consequently fusion protein comprising immunoglobulins (Curr Opin Immunol. 1997 Feb, Vol. 9(1): pp. 121-125, especially p. 121: column 1, paragraph 1). Therefore, Gray *et al.* do appreciate and teach that fusion proteins comprising modified CH2 domains confer increased circulating half-life as an innate response to decreased interactions with Fc receptors resulting from modified fusion proteins. Applicant's reliance on allegedly citing no difference in half-life between "CTLA4-IgG1" and "CTLA4IgG4" is improper. "CTLA4IgG4" has been incorrectly cited, the molecule Applicant cites by Gray *et al.*

actually has a modified IgG4 region and is referred to as "CTLA4IgG4m". As such, Applicant is drawing references to molecules not claimed and not addressed in the instant rejection. However, it is noted that Gray *et al.* clearly teach CLTA4IgG4 versus CTLA4IgG1 has decreased complement activation, which would result in a longer circulating half-life (column 10: lines 60-64). Furthermore, modifying the CH2 domain of Cγ1, Cγ2, Cγ3 and Cγ4 is taught to reduce "a biological effecter function...Fc receptor interaction" (column 4: lines 24-28).

Applicant's argument that the prior art references teach away from each other is not persuasive. Gillies *et al.* teaching of immunostimulatory fusion proteins and Gray *et al.* teaching of immunoinhibitory fusion proteins is taken out of context. The fact that Gillies *et al.* is using immunostimulatory molecules does not preclude this reference from being applied in the instant case because the reference teaches antibody-based fusion proteins comprising IL-2 were rapidly cleared. Rapid clearance indicates the fusion protein would have low or sub-optimal therapeutic value and efforts to decrease clearance rate, *i.e.* increase half-life, would increase the efficacy of the molecule. Improving pharmacokinetic parameters of the fusion protein by modifying CH2 domains of Cγ1, Cγ2, Cγ3 and Cγ4 as taught by Gray *et al.* provides a person of ordinary skill in the art motivation to combine the prior art references.

The rejection of claim 3, now applied to claim 1, as being unpatentable under 35 U.S.C. § 103(a) over Gillies *et al.* and Gray *et al.* in view of Winter *et al.* is maintained for the reasons of record in the previous office action (mail date: 09/30/2004). It is noted that Applicant has not set forth any particular arguments regarding the rejection of

record. If Applicant's intention was to rely on arguments set forth regarding rejections based on Gillies *et al.* and Gray *et al.*, attention is directed to the rationale and explanations set forth above.

Claim 4 is newly rejected under 35 U.S.C. 103(a) as being unpatentable over Gillies *et al.* in view of Gray *et al.* and Michaelsen *et al.* (US Patent No. 5,348,876). Gilles *et al.* and Gray *et al.* teach as set forth in the previous office action and above. Specifically, Gray *et al.* teach mutations at positions 234-237 in the IgG1 CH2 domain wherein mutations result in reduced Fc receptor binding (column 4: lines 28-32). Gray *et al.* further teach mutations in an IgG3 CH2 domain can likewise result in reduced "region mediated biological effector function" (column 4: lines 11-17). "Biological effector function" is defined to encompass Fc receptor binding (column 4: lines 26-27). Regarding Gillies *et al.*, antibody-based fusion proteins comprising IL-2 and immunoglobulins with a high rate of clearance are taught. However, Gillies *et al.* and Gray *et al.* do not teach antibody-based fusion proteins comprising an IgG3 CH2 domain with mutations at positions 281-283, 344 or 378.

Michaelsen *et al.* teach that IgG1 and IgG3 differ in both length and sequence in the hinge region. The IgG1 hinge sequence consists of 15 amino acids and the IgG3 hinge sequence consists of 62 amino acids (column 1: lines 13-15). Since it is known in the art that IgG1 and IgG3 have a high degree of sequence and function similarity, as evidenced by being classified in the same subclass of immunoglobulin molecules, compensating for minor sequences differences, such as gaps, as the one presented by Michaelsen *et al.* would be obvious to the skilled artisan to develop IgG3 mutants that

have reduced Fc receptor binding. Furthermore, when IgG1 and IgG3 are aligned taking into account gaps, positions 234-234 and 297 of IgG1, known mutations that decrease Fc receptor binding, line up with positions 281-284 and 344 of IgG3. Thus, Michaelsen *et al.* teach it would be obvious to the skilled artisan to derive IgG3 sequence mutations at positions 281-284 or 344 resulting in decreased Fc receptor binding from known IgG1 mutations with the same function.

It would have been obvious to a person of ordinary skill in the art at the time the invention was filed to combine the teachings of Gilles *et al.*, Gray *et al.* and Michaelsen *et al.* to make antibody-based fusion proteins comprising IL-2 and an IgG3 CH2 domain wherein the antibody-based fusion protein has decreased affinity for Fc receptors. One would be motivated to do so because Gillies *et al.* teach a utility for antibody-based fusion proteins comprising IL-2 and immunoglobulins. However, the antibody-based fusion proteins taught by Gillies *et al.* were cleared quickly from the blood, a problem that could be remedied by altering CH2 domains in IgG1 and IgG3. Finally, the expectation of success is reasonably assured based on teaching of Gillies *et al.* wherein modifications of IgG3, which could be derived from teaching by Michaelsen *et al.* as taught above, can reduce Fc receptor binding.

Conclusion

NO CLAIMS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **J. Jason Galvez, Ph.D**. whose telephone number is **571-272-2935**. The examiner can normally be reached Monday through Friday 9 AM to

5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Brenda Brumback, Ph.D.** can be reached at **571-272-0887**.

The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

JANET ANDRES
PRIMARY EXAMINER

JJG
06/10/2005